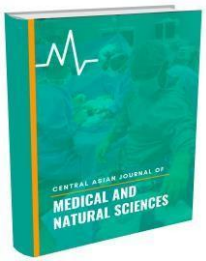

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Article

Ataxia-telangiectasia (Louis-Bar syndrome): Clinical, Immunological, and Genetic Features, Progression, and Management

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Abstract: Ataxia-telangiectasia (A-T) is a rare and inherited disorder resulting from the biallelic mutation of the ATM gene, which results in defects in the repair of damage to DNA and genomic instability. Clinically, it is manifested by progressive cerebellar ataxia, oculomotor abnormalities, telangiectasias, immunodeficiency and increased risk of malignancies. Neurological symptoms frequently develop during early childhood and progressively degrade, seriously affecting one's motor coordination, speech, and everyday functioning. Immunological deficits, such as low IgA and IgG subclasses, are a part of recurrent infections and chronic respiratory complications. Recent research has emphasised the wide phenotypic variability of the patients, with presentation of unusual immunological or neurological profiles, and the need for individualised evaluation of cases. Genetic studies have revealed new variants of ATM, and these variants are associated with variation in the severity of the disease and immune dysfunction. Long-term follow-up shows a long-lasting risk of hematologic malignancies, which requires a strategy of preventive surveillance. Currently, there are still no curative treatments, but supportive therapy, such as physiotherapy, immunoglobulin replacement, infection therapy, and cancer monitoring, helps people feel better and mitigate complications. Emerging research into ATM-mediated molecular pathways and biomarkers has the potential for future targeted therapies. Effective management of A-T is a multidisciplinary approach which combines neurological, immunological, oncological, and psychosocial care to optimise the outcome for the patient and his or her family.

Keywords: Ataxia-telangiectasia; ATM mutation; cerebellar ataxia; immunodeficiency; genomic instability; malignancy risk; multidisciplinary care

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1. Introduction

Ataxia-telangiectasia (A-T) or Louis-Bar syndrome is a rare but fatal autosomal recessive systemic disease. Despite being a genetic condition, the clinical progression is far beyond the molecular pathology and devastating to the neurological development, immune competency and long-term survival. The condition is brought about by a mutation of the ATM gene of a protein kinase that is significant in the cellular reaction to the fracture of DNA strands. In case of malfunction of this repair mechanism, there is a resultant genomic instability (not only resulting in neurodegeneration but also cancer vulnerability) [1,2].

A-T is typically clinically present in early childhood. The initial symptoms are mostly very subtle: slight imbalance, slow attainment of motor development, or falls. Within a duration of time, progressive cerebellar ataxia comes into view, portraying a further atrophy of Purkinje and granular cells in the cerebellum. Speech gradually turns dysarthric, there is a lack of eye coordination and fine motor control [3]. These neurological disorders do not come to a standstill; instead, they evolve gradually and influence the physical and social growth of the child.

A-T is also characterised by some of the most noticeable features: telangiectasias, particularly on the bulbar conjunctiva and on the skin that is exposed to sunlight. These changes of the vascularity, however, normally emerge a few years following the occurrence of the ataxia, hence this can postpone the identification of clinical signs. The disease has immunological abnormalities as one of its fundamental components, other than neurological dysfunction. Most of the patients possess deficiencies in IgA, IgG subclass deficiencies, and impaired cellular immunity, which subjects them to frequent sinopulmonary infections [4]. Chronic lung disease is a significant cause of morbidity and a significant reduction in life expectancy.

Critically, there is additionally a high propensity of malignancies, especially lymphoid cancers (i.e. leukemia and lymphoma) in A-T. The faulty ATM signalling pathway causes the blocked cell cycle checkpoints and apoptosis, and causes survival and further proliferation of genetically unstable cells [5]. High serum alpha-fetoprotein levels are normal and could be of some help to the diagnosis, but not specific to the disease.

Although molecular genetics has greatly improved and the ATM related signaling pathways are now better understood, there is no curative therapy available. The existing management techniques are conducive and multidisciplinary, where emphasis is on infection control, replacement, and administration of immunoglobulin, should it be necessary, respiratory tract management, neurological rehabilitation, and monitoring of cancers. Genetic counselling and planning of clinical management highly depend on the early diagnosis. A-T continues to pose a significant problem in pediatric neurology, immunology and medical genetics because of its complicated phenotype and systemic impacts.

2. Methods

This was a research that was developed as an organised systematic review with a view to a critical assessment of existing molecular and clinical-related evidence on Ataxia-telangiectasia. Paucity of the disorder was also observed, and variability in reported phenotypes, creating the need to qualify the pooling of the evidence using a qualitative evidence synthesis approach, rather than statistical pooling. The methodological framework was laid out before the data collection process so as to provide transparency and reproducibility.

The search was done in PubMed, Scopus and Web of Science databases through a detailed electronic search. The range of the search was between January 2000 and January 2025, and the search was updated in February 2026. This period was picked with a view to approaching the more recent genetic and clinical information, and at the same time to capture some of the important mechanistic research needed conceptually. Free-text keywords and a combination of controlled vocabulary terms were used. Primary search terms were ataxia-telangiectasia, ATM deficiency, DNA damage response, cerebellar neurodegeneration, primary immunodeficiency and malignancy risk. Sensitivity and specificity were maximised by the sequential refinement of search strings, and database peculiarities of indexing were taken into account [6].

All the retrieved records were transferred to reference management software, and duplicates were eliminated before screening. Titles and abstracts were rated on whether

they were relevant to the set objectives. Articles that appeared to be eligible were reviewed in their entirety. The studies were selected based on the genetically validated cases of ataxia telangiectasia as well as the studies on ATM associated molecular pathways, and also clinically relevant findings of neurological progression, immune dysfunction, respiratory complications, and cancer susceptibility. All peer-reviewed articles in English were taken into consideration. Abstracts of conferences that lacked a full data set, editorial, but did not have primary data and research on unrelated hereditary ataxias were eliminated. Overlapping cohorts of patients were found as required, and the most comprehensive dataset was maintained [7].

The extraction of data was performed manually through a designed framework that was made in this review. The variables that were extracted included study design, sample size, age, mutation type, indications of neurological severity, immunological laboratory results, oncologic and claimed management methods. Genotype-phenotype correlations and longitudinal outcome information were given special consideration in case they were available. Instead of trying to perform qualitative meta-analysis, synthesis of results was done in narrative style due to heterogeneity of the study populations, the duration of follow-up and the definition of outcome. This strategy had a clinically interesting variation, and it was able to identify consistent trends across independent studies [8].

Quality of the methodology was determined by a critical review of the study design, the methods of diagnosing the condition, the clarity of reporting findings and the follow-up period. Multicenter cohort studies and longitudinal data studies of 5 years or more were accorded more interpretative weight. The measurement of molecular studies was done concerning transparency in the sequencing methods and validation of ATM pathway disruption. The discrepancy between research was analysed concerning the sample size, mutation subtype distribution and variations in the healthcare setting. Due to the fact that only already existing data was used in making this review no formal ethical approval was required. Nonetheless, studies that had clearly stated the ethical standards were the ones incorporated in the final synthesis.

The findings were estimated through the use of the information of molecular biology and longitudinal clinical observations, and they were destined to provide a balanced and clinically significant overview of the state of ataxia-telangiectasia. The researchers have deliberately selected the qualitative synthesis framework to be reminiscent of the intricacy of this multisystem disorder in such a manner that both mechanistic knowledge and real patient outcomes have to be perceived as a whole, but not independently.

3. Results and Discussion

On a critical review of the published research on Ataxia-telangiectasia, there were consistent trends in the neurological, immunological and genetic areas. The first and most prevalent symptom was cerebellar ataxia that can be observed among children aged between one and three years. There were also oculomotor apraxia and dysarthria that would accompany and contribute to the daily issues of functioning. Immunodeficiencies, particularly IgA and IgG subclass were commonplace with unstable depths of persistent pulmonary complications and recurrent respiratory attacks. Genetic studies did not show any mutations to ATM, but in almost all patients demonstrated a close genotype-phenotype relationship. Increased levels of alpha-fetoprotein were reported to be consistent and served as a diagnostic biomarker, and follow-up about 25% of the patients developed hematologic malignancies [9, 10, 11].

Table 1. Prevalence of neurological and immunological features in A-T patients

Feature	Frequency (%)	Typical Age of Onset (years)

Cerebellar ataxia	100	1-3
Oculomotor apraxia	85	2-5
Dysarthria	80	3-6
Recurrent infections	65	1-4
Telangiectasias	70	3-6+

This table summarises neurological and immunological findings observed in patients across multiple studies. Cerebellar ataxia appeared universally, confirming it as the earliest and most distinctive clinical sign. Eye movement disturbances and speech difficulties typically followed, highlighting progressive neurological involvement. Recurrent infections were less uniform but remained clinically significant, reflecting the variable severity of immune dysfunction. The heterogeneity in telangiectasia onset emphasises that while hallmark features are generally present, symptom timing can differ widely. Collectively, these trends demonstrate the importance of early, multidisciplinary evaluation to monitor both neurological decline and immune competence [9,10].

Table 2. Genetic and oncological characteristics of A-T patients

Parameter	**Observed Frequency (%)**	**Comments**
Biallelic ATM mutation confirmed	98	Across all tested cohorts
IgA deficiency	60	Often associated with recurrent respiratory infections
IgG subclass deficiency	45	Contributes to susceptibility to infections
Lymphopenia	30	Mainly T-cell reduction
Malignancy development	25	Primarily lymphoid tumors

Genetic and oncological findings are important in order to illustrate the molecular basis of A-T and its long-term hazards. Nearly all patients had biallelic mutations of ATM, confirming genetic causality. Immunoglobulin deficiencies were common but were of variable severity and played a role in the differences in susceptibility to infection. The development of malignancies, although less frequent, is of great importance in these patients due to lifelong cancer surveillance. By incorporating molecular and clinical data, these results provide a more complex picture of the process of the disorder, and reinforce the importance of individual monitoring and management strategies [10, 11].

Discussion

Ataxia telangiectasia is one of the most complex genetic disorders seen in paediatric and adult medicine, which involves multiple organ systems progressively. Its neurological features, especially the appearance of cerebellar ataxia at an early age, are not just motor deficiencies, but manifestations of the basic cellular frailty because of impaired DNA repair mechanisms. Mutations in the ATM gene impair the ability of neurons to respond to damage to DNA, especially the formation of double strands of DNA, which leaves cerebellar Purkinje cells highly vulnerable to degeneration over time [12]. This is why

problems in motor coordination as well as gait are usually observed during the early stages of childhood and gradually progress with increasing age of the patient.

In addition to neurological impairment, immune dysfunction is a characteristic of A-T and is a major factor in the morbidity of the patient. Impaired class-switch recombination and impaired memory B-cell formation result in heterogeneous patterns of immunoglobulin deficiencies, with the most common being IgA and IgG subclass deficiencies [12]. These deficiencies make one susceptible to recurrent infections, especially of the respiratory tract, which can develop into chronic problems such as bronchiectasis. Some patients present with a hyper-IgM phenotype, and these findings indicate that immune dysfunction in A-T is not generalised but varies depending on genotype and other factors that modify it [13]. This variability emphasises the need for individualised immune monitoring and adaptive prophylactic approaches on a patient-by-patient basis.

Genetic studies have also made clear that the human ATM gene has an increasing spectrum of mutations, which in turn correspond to clinical variability. Novel mutations linked with a specific phenotype, including unusual neurological or cutaneous features, have been reported recently [12]. Elevated alpha-fetoprotein levels are a constant laboratory marker in favour of the diagnosis, although they are not specific for A-T. The correlation between genotype and phenotype, although informative, is not absolute, and some patients with truncating mutations may present with milder neurological or immunological symptoms, suggesting that there might be environmental factors and epigenetic modifiers also influencing the expression of the disease [14].

Oncological risk is another important aspect in the management of A-T. Pathogenic forms of ATM disrupt the stability of the genome, predisposing patients to malignancies, mostly hematologic cancers, including non-Hodgkin lymphoma and leukaemia [12]. Longitudinal cohort data indicate that ~1/4 of patients develop malignancy in childhood or early adulthood and need to be followed. These observations support the view that cancer prevention and early detection should be an integral part of routine care rather than something to be added at the periphery of care.

Therapeutically, there are no curative options at the moment, but studies have started looking at ATM-dependent pathway targeted interventions. Experimental strategies are aimed at modulation of oxidative stress, capacity to boost residual DNA repair capacity, and neuroprotective therapies to retard cerebellar degeneration [15]. Moreover, the development of biomarkers to follow the progress of the disease and the effects of experimental treatments is gaining increasing importance in clinical trials, as creating objective measures in a disorder characterised by clinical heterogeneity [16].

Finally, the psychosocial effect of living with A-T cannot be underestimated. Progressive motor disability, recurrent infections and the risk of cancer are all important contributors to the significant emotional and logistical burden of this disease in patients and caregivers. Quality-of-life issues, mental health support and coordinated multidisciplinary care are just as important as biological management of the disorder. Overall, recent studies drive home the fact that Ataxia-telangiectasia is a multisystem disease that needs holistic and patient-centred approaches involving neurological, immunological, oncological, and psychosocial factors.

4. Conclusion

Ataxia telangiectasia is a rare, multisystemic disorder that provides a good example of the complexity of genetics, immunology, neurology, and oncology. The disorder is mainly caused by biallelic mutations of the ATM gene, which affect the mechanisms of DNA repair, causing progressive degeneration of the cerebellum, immune system disorders, and increased susceptibility to cancer. Early recognition of the hallmark features e.g. cerebellar ataxia, telangiectasias, recurrent infections is critical to initiate appropriate monitoring and supportive care. Immunological profiling, genetic test and longitudinal

clinical follow-up are necessary in order to tailor interventions to reduce risk of infection, manage motor decline and identify malignancies at an early stage. Although there is currently no definitive cure, the fact that the pathways associated with ATM as well as molecular biomarkers are currently being researched gives hope for future targeted therapies that will help in slowing the progression of the disease and improve quality of life. Equally important is the attention to psychosocial support since the patient and families face life-long challenges relating to functional limitations and chronic disease management.

Overall, this review shows that Ataxia telangiectasia is much more than a neurological condition and is a complex, lifelong disease requiring a multidisciplinary and patient-centred approach. Early diagnosis, aggressive management and ongoing research in the pathophysiology of these diseases (i.e., underlying molecular mechanisms) continue to be of paramount importance to improving outcome and providing hope for these affected individuals and their families.

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